Please substitute the hereto attached Abstract for the originally filed Abstract sheet.

IN THE CLAIMS

Please amend the claims as follows:

24. (amended) A pharmaceutical composition comprising a cytotoxin-conjugated anti-Tac [preparation] antibody, wherein the cytotoxin is selected from the group consisting of ^{90}Y and ricin A, and a suitable excipient, provided in an effective dose.

25. (amended) The ~~pharmaceutical~~ composition of claim 24 wherein the cytotoxin conjugated anti-Tac [preparation] antibody comprises ^{90}Y-conjugated anti-Tac, wherein the effective dosage comprises 2-100 mg anti-Tac wherein 5-15 mCi ^{90}Y conjugate [is provided].

REMARKS

Applicants respectfully request favorable reconsideration in view of the herewith presented amendment and remarks.

Claims 1-25 are pending in the instant patent application.

The Examiner has requested that the specification be amended to include a claim of priority. Applicant has amended the specification accordingly. Hence this rejection is believed moot.

The Examiner has requested that applicant change the title of the invention. Applicant has amended the title. Therefore, this objection is believed to be moot.

The Abstract has been objected to as not adequately describing the claimed invention. Applicant respectfully traverses this objection. The claims and the abstract are directed to methods of treating malignancies and autoimmune disorders using either conjugated anti-Tac or conjugated and unconjugated anti-Tac. While applicant does not agree with this objection, a new abstract is presented herewith which is urged to be adequate.

Claims 24-25 have been rejected under 35 U.S.C.§112, second paragraph, as failing to particularly point out the claimed invention in the recitation of "anti-Tac preparation". In addition, claim 25 has been rejected as indefinite in the recitation of "wherein the effective dosage ... is provided". Applicant has amended the claims and hence, urges the Examiner to reconsider and withdraw this rejection.

Claim 24 is rejected under 35 U.S.C. §102(b) as being anticipated by Kozak et al. in that Kozak teaches ^{212}Bismuth-labeled anti-Tac monoclonal antibody. Applicant respectfully disagrees with this rejection. However, in order expedite this case to allowance, applicant has amended the claim. The Examiner is respectfully requested to reconsider and withdraw the §102(b) rejection.

Kozak describes the use of an α-emitting radionuclide. ^{212}Bi has a physical half-life of only one hour. This half-life is too short to be delivered effectively by a monoclonal antibody to most tumor targets. Further, the method used to link the ^{212}Bi to the antibody is not useful in producing a ^{90}Y conjugate, since the ^{212}Bi linking method, described in Kozak, produces an unstable conjugate. Stability of the conjugate is critical to the successful use of the conjugates of the present invention. The Kozak method does not teach or suggest either the use of ^{90}Y or any β-emitting radionuclide or a method of stably linking

a β-emitting radionuclide to an anti-Tac antibody. Therefore, the claim 24 is neither taught or suggested by Kozak. The Examiner is respectfully requested to reconsider and withdraw the §102(b) rejection.

Claims 1-14, 16, 17 and 19-25 have been rejected under 35 U.S.C.§102(b) as anticipated by or in the alternative, under 35 U.S.C. §103 as obvious over Waldmann (Ann. Oncol., 1994). Applicant respectfully disagrees with this rejection.

The Examiner alleges that the claimed dosages are "either taught by the references cited in this review article, or it would have [been] obvious to one or ordinary skill in the art at the time the invention was made". However, the Examiner also admits that Waldmann is "silent about the effective dosages per se". Applicant urges that the cited Waldmann reference does not provide any teaching or suggestion relating to the claimed effective dosage; i.e. the amount of anti-Tac conjugated to the specific amount of ^{90}Y. The Examiner merely states that the "references cited in the review article" disclose or make obvious the effective dosage. However, the Examiner fails to identify any particular teaching of any particular reference cited in the review article which teaches the effective dosage. The initial burden of making a prima facie case is upon the Examiner and failing to cite evidence does not meet the Examiner's burden. It might be noted that anticipation requires exact disclosure in a single reference. The reference by the Examiner to citations within the relied-upon reference is not the citation of a single reference. Without a teaching or suggestion of the effective dosage, the art cited by the Examiner describes little more than the subject matter of the original priority application, from which this application claims

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benefit under 35 U.S.C. §120. For these reasons, applicant respectfully requests reconsideration and withdrawal of the §§102/103 rejection.

Claims 1-14, 16, 17 and 19-25 have been rejected under 35 U.S.C.§102(b) as anticipated by or in the alternative, under 35 U.S.C. §103 as obvious over Waldmann et al. (Important Adv. Oncol. 1994). Applicant respectfully disagrees with this rejection.

This review article describes the use of 0.5 mg/kg-1.5 mg/kg unconjugated anti-Tac antibody in the treatment of GVHD (p. 136, col. 1). Later in this review article, Waldmann describes the use of 5-15 μCi ^{90}Y-conjugated anti-Tac antibody in treatment of ATL (p. 138, col. 1). There are 1000 μCi in 1 mCi: therefore, 5-15 μCi is equal to 0.005-0.015 mCi. This is a 1000-fold lower radionuclide level than claimed in the present invention. Further, if the skilled artisan were to combine the GVHD treatment doses of 0.5 mg/kg-1.5 mg/kg of anti-Tac antibody with the radionuclide recommendations of the ATL treatment, i.e. 5-15 μCi ^{90}Y, the skilled artisan would be administering a conjugate whose specific activity is much too low to have an effective cytotoxic effect on cells. That is, there would be too much antibody and far too little ^{90}Y to be effective as a cytotoxic agent. Therefore, the skilled artisan would not be able to deduce the claimed effective dosages from this review article. In effect, the reference cited by the Examiner neither exactly teaches nor suggests the presently claimed subject matter. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-14, 16, 17 and 19-25 have been rejected under 35 U.S.C.§102(b) as anticipated by or in the alternative, under 35 U.S.C. §103 as obvious over Waldmann (Leukemia, 1993). Applicant respectfully disagrees with this rejection.

The Examiner alleges that the claimed dosages are "either taught by the references cited in this review article, or it would have [been] obvious to one or ordinary skill in the art at the time the invention was made". However, the Examiner also admits that Waldmann is "silent about the effective dosages per se". Applicant urges that the cited Waldmann reference does not provide any teaching or suggestion relating to the claimed effective dosage; i.e. the amount of anti-Tac antibody conjugated to a specific amount of ^{90}Y. Further, the Examiner merely states that the "references cited in the review article" disclose or make obvious the effective dosage. The initial burden of making a prima facie case is upon the Examiner and failing to cite evidence does not meet the Examiner's burden. However, the Examiner fails to identify any particular teaching of the effective dosage. Without such a teaching or suggestion, the art cited by the Examiner describes little more than the subject matter of the original priority application, from which this application claims benefit under 35 U.S.C. §120. In effect the reference cited by the Examiner neither exactly teaches nor suggests the presently claimed subject matter. For these reasons, applicant respectfully requests reconsideration and withdrawal of the §§102/103 rejection.

It is noted that both the Waldmann (Ann. Oncol.) and Waldmann (Leukemia) references describe the use of 10 mCi doses of ^{90}Y-conjugated anti-Tac. However, the references do not teach or suggest the <u>amount</u> of anti-Tac conjugate for each dosage. This is important to note, since the treatment disclosed in the present invention is not simply a

matter of the amount of radionuclide administered, but rather it is the combination of an appropriate amount of anti-Tac and the appropriate amount of ^{90}Y radionuclide. The cited references do not teach or suggest the amount of anti-Tac antibody to be administered as claimed. One skilled in the art would not know how much anti-Tac antibody to conjugate to the 10 mCi ^{90}Y to produce an effective treatment, since there is no teaching or suggestion as to the amount of anti-Tac antibody.

If the skilled artisan were to combine either of these two review articles with Waldmann (Important Adv. Oncol.) reference, the artisan would still be at a loss. As discussed above, if the skilled artisan were to use the amount of anti-Tac recommended for GVHD treatment at the radionuclide levels recommended for ATL treatment, the artisan would have a dosage which is ineffective as a cytotoxic agent. There is no teaching or suggestion in any of these Waldmann references to use the specific amount of anti-Tac conjugated to the specific amount of ^{90}Y, as set forth in the claims. For these reasons, none of the Waldmann review articles teaches or suggests the specific effective dosage claimed in the instant application. Reconsideration and withdrawal of these §102/103 rejections is respectfully requested.

Claims 1-14 and 16-25 have been rejected under 35 U.S.C. §103 as obvious over Waldmann (Ann. Oncol. 1994) or Waldmann et al. (Important Adv. Oncol. 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993) and Kreitman et al. (Bioconj. Chem. 1993). Applicant respectfully disagrees with this rejection.

As discussed above, the three Waldmann review articles fail to provide the skilled artisan with sufficient guidance to render the claimed invention obvious without undue experimentation. There is no teaching or suggestion regarding the effective dosage; i.e. the amount of anti-Tac conjugated to a specific amount of ^{90}Y. Without such a teaching or suggestion, the art cited by the Examiner discloses little more than the original priority application, from which the instant application claims benefit.

Hakimi et al describe a dose escalation study and the pharmokinetic effects of unconjugated anti-Tac antibody. The antibodies used in this study were not conjugated to any radionuclide. Rather, the anti-Tac antibodies were administered in dosages from 0.05 mg/kg to 5 mg/kg. This treatment regime is designed to block the immunogenic response in autoimmune disease and graft rejection disease. This regime is NOT a cytotoxic treatment as is the treatment method of claim 1. ^{90}Y is a radionuclide which provides a cytotoxic agent to the anti-Tac antibody, which is capable of targeting certain tumor cells. Hakimi does not teach or suggest an effective dosage for the cytotoxic treatment of cells having elevated levels of Tac-antigen. There is no teaching or suggestion of the ^{90}Y to be used to generate the treatment of the claimed invention. If the skilled artisan would attempt to combine the Waldmann references, one of which describes use of 5-15 μCi and the others which describe use of 10 mCi, the artisan would have no way of pinpointing the proper specific activity of the conjugate with any reasonable expectation of success.

Similarly, Waldmann (Blood, 1993) describes the administration of unconjugated anti-Tac antibody for the treatment of ATL. The doses used -- 2 times 20 mg anti-Tac during the first week, and 2 times 40 mg anti-Tac during the second week -- are

strikingly similar to the doses disclosed in the original priority application, from which the instant application claims benefit. In addition, as shown in Table 2 of the Waldmann (Blood) reference, most of the doses used in the study (ranging from 60 to 500 mg) far exceed the amount of anti-Tac presently claimed. Also, the dosages claimed in instant claim 1 require ^{90}Y as the radionuclide cytotoxic agent. Waldmann, like Hakimi, does not teach or suggest the use of a radionuclide conjugated anti-Tac. Therefore, if the skilled artisan were to combine the Waldmann review articles with Hakimi and Waldmann (Blood), the artisan could not identify the claimed dosages without undue experimentation.

Further, the Examiner has combined the above references with Kreitman et al. This reference describes the use of *Pseudomonas* exotoxin conjugated to anti-Tac in mice and cultured human cells. The doses described by Kreitman are directed to the use of the conjugate in mice or tissue culture and NOT for use in humans, as claimed. There is no teaching or suggestion of a therapeutically effective dose for use in humans. Therefore, Kreitman, if combined by the skilled artisan with the Waldmann review articles, the Waldmann (Blood) reference and Hakimi still does not provide the skilled artisan with sufficient guidance to identify the dosages of the instant claims with any reasonable expectation of success. Deduction of the instant dosage ranges would require undue experimentation, because of the broad and inconsistent ranges used in these cited references. Therefore, applicant respectfully requests reconsideration and withdrawal of the §103 rejection.

In addition, the Examiner has asserted that the use of a two step method of treatment, wherein the anti-Tac is a ^{90}Y conjugate in the first step and the anti-Tac is

unconjugated in the second step would be obvious because of the common known purpose and the known toxicity of the conjugated anti-Tac antibodies. Applicant respectfully disagrees with this obviousness rejection. None of the references cited by the Examiner teach or suggest the use of a two step method of treatment. In this regard, applicant requests that the Examiner provide either citation to appropriate references suggesting a two step method of treatment, as contemplated by 37 CFR §1.107(a), or an affidavit of information within his personal knowledge, as contemplated by 37 CFR §1.107(b). In the absence of a countervailing evidentiary showing by the Examiner, the rejection is incomplete, since none of the references cited by the Examiner, alone or in combination teach or suggest the claimed invention. Reconsideration and withdrawal of the §103 rejection is respectfully requested.

Claim 15 has been rejected under 35 U.S.C. §103 as obvious over Waldmann (Ann. Oncol. 1994) or Waldmann et al. (Important Adv. Oncol. 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993) and Kreitman et al. (Bioconj. Chem. 1993) as applied to claims 1-14 and 16-25 and in further view of Parenteau et al. (Transplantation). Applicant respectfully disagrees with this rejection.

As set forth above, the Waldmann review articles do not teach or suggest the dosages claimed. In fact, because of the broad and inconsistent ranges employed in the review articles and in Waldmann (Blood), Hakimi and Kreitman, the skilled artisan would not be able to identify the dosage range claimed without extensive and undue experimentation. Without such a teaching or suggestion, the rejection is incomplete.

Parenteau et al has been cited by the Examiner as disclosing the use of G-CSF in combination with ^{90}Y-conjugated anti-Tac antibody treatment. However, none of the articles cited by the Examiner alone or in combination would lead the skilled artisan to a reasonable expectation of success in selecting the correct amount of anti-Tac, conjugated to the correct amount of ^{90}Y without undue experimentation. The articles relied upon by the Examiner set forth such a broad and inconsistent range of anti-Tac and ^{90}Y amounts, there would be no reasonable expectation that a skilled artisan would arrive at the claimed invention. Parenteau does not remedy this problem, since their studies were conducted on monkeys and used 1.6 mg/kg anti-Tac, which translates to approximately 112 mg for an average 70 kg human. This amount of anti-Tac exceeds the claimed range. In addition, there is no description of the specific activity of the ^{90}Y-conjugate; i.e. the amount of radionuclide in the conjugate. Therefore, the skilled artisan still be unable to identify the correct range of anti-Tac having the correct amount of ^{90}Y conjugated to it. For these reasons, applicant respectfully requests reconsideration and withdrawal of the §103 rejection.

Claims 25 and 26 have been rejected under 35 U.S.C.§103 as obvious over Kozak et al or Diamantstein et al in view of Order et al or Wessels et al. Applicant respectfully disagrees with this rejection.

Kozak teaches that anti-Tac, a monoclonal antibody (MAb) directed to the human interleukin 2 (IL-2) receptor, can be conjugated to an α-particle emitting radionuclide, ^{212}Bi, by use of a bifunctional ligand. The ^{212}Bi-conjugated MAb is disclosed to have potential value as a cytocidal reagent for radioimmuno-therapy of patients with adult T-cell

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leukemia. It is also noted that the ^{212}Bi-conjugate may have value in the treatment of various autoimmune diseases and in organ transplantation protocols.

The Diamantstein citation relates to an attempt to find an IL-2 receptor targeted immunosuppressive therapy. This review article discusses only the IL-2 receptor and approaches to immunosuppressive therapy using anti-IL-2 receptor monoclonal antibodies. There is no discussion of the use of any radionuclides in immunosuppressive therapy.

Order teaches the possible use of ^{90}Yttrium chelated to anti-ferritin antibodies for the treatment of hepatocellular cancer. External radiation (900 rad) to the primary tumor in advance of the use of ^{90}Y-antiferritin provided increased antibody uptake and increased tumor dose rate and total dose. It is noted at page 280 last paragraph that the hepatoma is the ideal tumor to study the dosimetry of radiolabeled antibody and it is speculated that ^{90}Y radiolabeled antibodies "may have" an impact in "radiation oncology".

Wessels is an abstract in which an absorbed dose calculation comparison has been computed for radiolabeled tumor-associated antibodies. The abstract notes that Re-186 and Y-90 "...have been determined to be among the best therapy radiolabels...". Only the abstract and not the full article was cited and relied upon by the Examiner.

As an initial matter, it is well-known that an Examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done.

Diamantstein is merely a review article discussing the interleukin-2 receptor and approaches to selective immunosuppressive therapy by anti-IL-2 receptor monoclonal antibodies. However the review article is completely silent on the use of radionuclides in immunosuppressive therapy. Therefore, it is urged that Diamantstein's review article is not directly pertinent in evaluating the prior art concerning radioimmunosuppressive therapy methods.

In this sense, Diamantstein does not anticipate effective therapy such as contemplated in the present method and is not relevant with respect to the objective of the present invention. This is recognized in the Kozak citation relied upon by the Examiner.

Kozak teaches the use of anti-Tac monoclonal antibodies conjugated with the α-emitting radionuclide, ^{212}Bismuth, as modalities for radioimmunotherapy. There is no disclosure of the in vivo use of anti-Tac monoclonal antibodies conjugated with a β-emitting radionuclide.

Kozak seeks to find a more effective treatment than the use of unmodified anti-Tac. In this citation, it was taught that radionuclide ^{212}Bi, an alpha particle emitting isotope could be conjugated to anti-Tac.

Kozak teaches that ^{212}Bi should be effective since this radionuclide releases high energy over a short distance and has low penetrability. Additionally, Kozak notes that the 1-hr half life of ^{212}Bi makes it appropriate for rapid targeting to leukemic cells without prolonged exposure to normal tissue.

Kozak notes that:

> There are numerous α-, β- and γ-emitting radioisotopes that are suitable for different forms of therapy."

It is further stated that:

> "Our selection of an α-particle - emitting radionuclide for immunotherapy was based on the radiobiological properties of α-particle - emitting radionuclide."

Additionally, Kozak teaches that:

> "...^{212}Bi is particularly well-suited for the treatment of circulating leukemic cells... Thus, α-particle - emitting radionuclides coupled to specific antibodies such as anti-Tac represent a modality of potential use in immunotherapy."

It is clear that Kozak does not contemplate the use of β-emitting radionuclide. Kozak clearly selected the α-emitting radionuclide as the most preferred radionuclide for radiotherapy targeting activated T-cells, i.e., radioimmunosuppressive therapy. Kozak suggests that α-emitting particles would be PREFERRED to β-emitting particles for radioimmunosuppressive therapy, while β- or γ-emitting particles for radioimmunosuppressive therapy, could be "suitable for different forms of therapy". Such a teaching actually leads away from the present invention, in that it would discourage the skilled artisan from using β-emitting particles for radioimmunosup-pressive therapy. It should also be noted that Kozak teaches γ-emitting particle should be used in the treatment of circulating leukemia cells. This should be contrasted with the Examiner's assertion vis a vis Order reference in which a β-emitter is used in the treatment of liver carcinoma.

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Contrary to the Examiner's assertion, Kozak made a specific choice to use α-particle - emitting radionuclides for immunotherapy and did not simply limit their report to α-particle - emitting radionuclides as the main subject. A conscious selection for specific reasons was made.

Order teaches the use of ^{90}Yttrium conjugated to an anti-ferritin antibody in radiotherapy of hepatocellular cancer. Ferritin is a long-lived intracellular housekeeping iron-storage protein found primarily in the liver. Radiotherapy targeting ferritin will encounter very different considerations than those encountered with the development of radioimmunosup-pressive therapy. Radioimmunosuppressive therapy targets the IL-2 receptor which is a transiently expressed, extracellular protein found on circulating, activated T-cells. In fact, the use of a β-emitting radionuclide such as ^{90}Yttrium in a "different form of therapy" such as hepatocellular cancer clearly follows the teachings of Kozak as quoted above. However, Order can in no way be said to make the use β-emitting radionuclides in immunosuppressive therapy obvious. There is no teaching or suggestion of using a β-emitting particle, such as ^{90}Yttrium in radioimmunosuppressive therapy, nor is there any teaching or suggestion equating radiotherapy treatment with radioimmunosup-pressive treatment. Absent such a suggestion, the skilled artisan would have no basis for making the proposed combination.

Wessels teaches that there are a number of radionuclides suitable for use in radiotherapy of tumors. However, the article does not specify which radionuclides would be preferred for specific targets. Clearly, there will be a difference in selection of a radionuclide depending upon what type of protein or organ is being targeted. For example, a

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different radionuclide may well be selected if the protein being targeted is intracellular and has a long half-life as opposed to a protein that is transiently expressed on the surface of a circulating cell.

Furthermore, the Wessels paper discusses ^{90}Y in general terms but does not consider the critical methods required for the linkage of ^{90}Y to the monoclonal antibody. ^{90}Y is a bone-seeking metal that, if allowed to enter into bone, leads to bone marrow irradiation and unacceptable bone marrow toxicity. This effect is seen for Order who noted that ^{90}Y caused toxicity to the hematopoietic system, i.e., the site of the formation of blood or blood cells, bone marrow. It might be noted that T-cells are produced in the lymph nodes and are present in the circulatory system. Toxicity to the hemopoietic system may have made bone marrow a possible target for ^{90}Y therapy. However, this disclosure would neither teach nor suggest antibody radionuclide therapy using ^{90}Y with respect to the target area of the present claims.

It is respectfully urged that the cited references either alone or in combination, fail to teach or suggest combining a β-emitting particle, such as ^{90}Yttrium with an antibody specific for the Tac antigen in a radioimmunosuppressive treatment. In fact, the Kozak reference suggests that α-emitting particles should be used for immunosuppressive therapy, thereby leading away from the present invention. Neither Order nor Wessels relate to radioimmunosuppression and the Examiner has failed to support the premise that cancer therapy and radioimmunosuppression are equivalent.

Claims 1-25 have been provisionally rejected for obviousness-type double patenting as being unpatentable over claims 1-5, 13, 22 and 28 of copending application serial no. 07/879,056 in view of Waldmann (Ann. Oncol. 1994) or Waldmann et al. (Important Adv. Oncol. 1994) or Waldmann (Leukemia, 1993).

Applicant respectfully traverses the obviousness-type double patenting rejection, since the claims of the copending application serial no 07/879,056 have not yet been allowed. Should these claims be allowed and issue into a U.S. patent, applicant will file a terminal disclaimer at that time.

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

No additional fee is believed to be necessary.

The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2026-4003US3.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition and for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 2026-4003US3.

A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: Dec. 03, 1996

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